

# Diabetes: preventing coronary heart disease in a high risk group

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Cardiovascular disease is the major cause of morbidity and mortality in patients with type 2 diabetes. Numerous outcome trials have demonstrated clinical benefits from effective treatment of individual cardiovascular risk factors in patients with diabetes. These trials have provided the basis for current treatment guidelines and targets. More recently, multifactorial intervention strategies have shown a reduction in both cardiovascular and microvascular events in patients with type 2 diabetes. However, full implementation of a truly multifactorial strategy into routine practice remains an ideal due to practical difficulties of sustained implementation and associated costs. These practical issues relating to the treatment of diabetes and its complications are now in a greater spotlight due to the growing number of patients requiring treatment.



In the management of patients with diabetes, it is important to consider that the reduction of risk is not focused on one complication but is directed at reducing the risk of several complications. Diabetes is associated with an exaggerated risk of both microvascular and macrovascular complications.

**Microvascular disease prevention**—A reduction in the specific diabetes (or microvascular) complications of retinopathy, nephropathy and neuropathy was shown with improved glycaemic control in patients with type 1 diabetes in the diabetes control and complications trial (DCCT),<sup>1</sup> and in type 2 diabetes in the UK prospective diabetes study (UKPDS). Even when the lower target levels of glycaemic control are not achieved, but there is improved glycaemia, it is possible to obtain benefit with regard to delaying both the onset of complications and their progression.

**Macrovascular disease prevention**—Among patients with type 2 diabetes, cardiovascular disease accounts for 70–80% of mortality, with around 15% of patients dying from stroke. Coronary heart disease rates are 2–6 fold higher than in the non-diabetic population and there is a loss of pre-menopausal protection among diabetic women. The strength of the relation between cardiovascular risk factors and coronary heart disease is similar to non-diabetics but is at a higher level.

In recent years, a number of intervention trials have provided strong evidence of the benefits from effective treatment of individual risk factors in patients with diabetes.

## UNIFACTORIAL INTERVENTIONS

### Glucose

Diabetes is characterised by a state of chronic hyperglycaemia resulting from environmental and genetic factors. Due to the high cardiovascular risk associated with diabetes, a contemporary definition of diabetes has been proposed: “a state of premature cardiovascular death which is associated with chronic hyperglycaemia and may also be associated with blindness and renal failure.”<sup>2</sup>

The UKPDS has provided extensive information on the treatment of type 2 diabetes. This study ranked the five most important predictors of coronary heart disease: (1) increased concentrations of low density lipoprotein cholesterol; (2) decreased concentrations of high density lipoprotein (HDL) cholesterol; (3) hyperglycaemia; (4) raised blood pressure; and (5) smoking (table 1).<sup>3</sup>

The study has provided important information regarding the treatment of hyperglycaemia and hypertension. Lowering of blood glucose, either with sulfonylureas or insulin, resulted in only a modest reduction of coronary disease that just failed to achieve statistical significance.<sup>4</sup> By comparison, treatment of hyperglycaemia with metformin in obese and overweight patients significantly reduced coronary heart disease as well as reducing diabetes related end points and all cause mortality by one third.<sup>5</sup>

In the comparison between blood pressure lowering and glucose lowering in UKPDS, table 2 shows that modest reductions in blood pressure (a 10/5 mm Hg difference in blood pressure) prevented three times as many diabetes related events than modest reductions in glycaemia (a 1% difference in HbA<sub>1c</sub>).<sup>6</sup>

### Blood pressure

A number of trials have now been published regarding the treatment of hypertension in patients with diabetes. One of the trials, the hypertension optimal treatment (HOT) trial, is of particular interest.<sup>7</sup> Patients were randomised to three different blood pressure targets (diastolic blood pressure < 90 mm Hg, < 85 mm Hg, or < 80 mm Hg). Although there was no difference in event outcome between non-diabetic patients randomised to the three targets, among the diabetic subjects randomised to target diastolic blood pressure < 80 mm Hg there was a 51%

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**Abbreviations:** CI, confidence interval; DCCT, diabetes control and complications trial; HDL, high density lipoprotein; HOT, hypertension optimal treatment; HR, hazard ratio; LDL, low density lipoprotein; UKPDS, UK prospective diabetes study; VA-HIT, Veterans Affairs high-density lipoprotein cholesterol intervention trial

**Table 1** Stepwise selection of risk factors for coronary artery disease, adjusted for age and sex, in 2693 subjects with new type 2 diabetes followed for median 7.9 years

Coronary artery disease (n = 280)		
Position in model	Variable	P Value
First	LDL cholesterol	<0.0001
Second	HDL cholesterol	0.0001
Third	Haemoglobin A <sub>1c</sub>	0.0022
Fourth	Systolic blood pressure	0.0065
Fifth	Smoking	0.056

HDL, high density lipoprotein; LDL, low density lipoprotein.  
Adapted from Turner *et al.*<sup>3</sup>

reduction in event outcome compared with the < 90 mm Hg group ( $p = 0.005$ ), despite the fact that there was only a 4 mm Hg difference in achieved blood pressure. The study also showed that the use of aspirin 75 mg in diabetic subjects receiving effective blood pressure lowering treatment was associated with a further 15% event reduction ( $p = 0.03$ ).

Several blood pressure lowering trials have highlighted the fact that multiple drug treatment is required to achieve effective blood pressure lowering and the consequent cardiovascular benefit. In the HOT trial, 69% of patients were on at least two drugs, while in UKPDS, 70% of patients were taking two or more antihypertensive drugs and 29% of patients were taking three or more drugs to achieve the blood pressure targets.

On the basis of recent clinical trials, the current British Hypertension Society recommends a target blood pressure of < 140/80 mm Hg for patients with diabetes.<sup>8</sup> The National Institute for Clinical Excellence has accepted the same target for patients with diabetes, with a lower target of 135/75 mm Hg in the presence of microalbuminuria or proteinuria.<sup>9</sup> However, hypertension targets in other parts of the world are already lower than this. The latest guidelines from the European Society of Hypertension and the European Society of Cardiology,<sup>10</sup> and the seventh report from the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7) in the USA, have both lowered the target to < 130/80 mm Hg for patients with diabetes.<sup>11</sup>

Clearly, achieving such targets poses a therapeutic challenge, not only because of the cost of drug treatments with the increase in numbers to be treated but also because of patient compliance factors. In the 1998 UKPDS results, one third of patients in the atenolol group and a quarter of those taking angiotensin converting enzyme (ACE) inhibitors were non-compliant or had adverse effects from medication.<sup>12</sup> Therefore, tailoring each treatment to individual patients is important.

**Table 2** Modest reductions in blood pressure prevented more diabetes related events than modest reductions in glycaemia

Intensive glucose control (HbA <sub>1c</sub> 7% v 7.9%)		
Diabetes related end point	-12%	$p = 0.029$
Microvascular end points	-25%	$p = 0.099$
Myocardial infarction	-16%	$p = 0.052$
Tight blood pressure control (144/82 mm Hg v 154/87 mm Hg)		
Diabetes related end point	-24%	$p = 0.0046$
Microvascular end points	-37%	$p = 0.0092$
Myocardial infarction	-21%	$p > 0.05$
Heart failure	-56%	$p = 0.0043$
Stroke	-44%	$P = 0.013$

Adapted from UKPDS 33<sup>4</sup> and UKPDS 36.<sup>6</sup>

**Table 3** Coronary heart disease in subgroups of patients with diabetes in the statin trials

Study	Drug	Number (in diabetes subgroup)	CHD risk reduction (in overall study)	CHD risk reduction (in patients with diabetes)
<i>Primary prevention</i>				
AFCAPS/	Lovastatin	155	37%	43% (NS)
TexCAPS <sup>13</sup>				
HPS <sup>14</sup>	Simvastatin	5963	27%	27% ( $p < 0.0001$ )
<i>Secondary prevention</i>				
CARE <sup>15</sup>	Pravastatin	586	23%	25% ( $p = 0.05$ )
4S <sup>16</sup>	Simvastatin	202	32%	55% ( $p = 0.002$ )
LIPID <sup>17</sup>	Pravastatin	782	24%	19% (NS)
4S (reanalysis) <sup>18</sup>	Simvastatin	483	32%	42% ( $p = 0.001$ )
LIPS <sup>19</sup>	Fluvastatin	202	22%	47% ( $p = 0.04$ )

## Lipids

Table 3 summarises the benefits of lipid management seen in diabetes patients within the major primary and secondary prevention studies. In most cases, the benefits from low density lipoprotein (LDL) cholesterol lowering with statin treatment in clinical event reduction seem to be either equal to or greater than the benefit in non-diabetic patients.<sup>13–19</sup>

Fibrates also have a lipid lowering role in patients with diabetes. These drugs specifically target the characteristic dyslipidaemia of diabetes—raised triglyceride and lowered HDL cholesterol concentrations. The Veterans Affairs high-density lipoprotein cholesterol intervention trial (VA-HIT) enrolled men with existing coronary heart disease and a diabetic like dyslipidaemia and randomised them to the fibric acid derivative gemfibrozil or placebo.<sup>20</sup> At five years follow up, the fibrate was associated with a 22% reduction in non-fatal myocardial infarction or death from coronary causes ( $p = 0.006$ ). The benefit was similar among the diabetic subjects to that observed in the total cohort.

It is worth noting that even in the statin trials, a large number of clinical coronary events occur despite LDL lowering. Stratification of coronary events according to patients' baseline HDL cholesterol value indicates that more events occur (irrespective of whether patients receive a statin or placebo) in those with lower concentrations of HDL cholesterol.<sup>21</sup> This may be particularly important in diabetes where the type 2 diabetic state is characterised not only by hyperglycaemia but also by a dyslipidaemia with a raised serum triglyceride and low HDL. It is possible that targeting this metabolic profile in the future will be able to reduce clinical coronary events further.

## MULTIFACTORIAL RISK FACTOR INTERVENTIONS

One of the most important trials in cardiovascular and microvascular risk prevention in patients with type 2 diabetes was recently published and involved a multifactorial intervention strategy.<sup>22</sup> The Steno-2 study investigators randomised 160 patients to receive either conventional general practitioner care based on national guidelines or intensive therapy, which involved patients and their partners being seen every three months by at least three members of the multidisciplinary diabetes team (doctor, nurse, and dietician) and receiving lifestyle advice and drugs to achieve lower treatment targets for hyperglycaemia, hypertension, and dyslipidaemia.

After a mean 7.8 years of follow up, cardiovascular events were halved (hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.24 to 0.73) and there were significant reductions in rates of retinopathy (HR 0.42, 95% CI 0.21 to 0.86), nephropathy (HR 0.39, 95% CI 0.17 to 0.87), and autonomic neuropathy (HR 0.37, 95% CI 0.18 to 0.79). Importantly, the

**Table 4** Diabetes prevention studies

Study	Intervention	Risk reduction (%)
Da Qing study <sup>23</sup>	Lifestyle (diet, exercise, diet + exercise) for 6 years	31 (diet) 46 (diet + exercise) 42 (exercise)
Finnish diabetes prevention study <sup>24</sup>	Lifestyle (diet and exercise) for 4 years	58
Diabetes prevention program <sup>25</sup>	Lifestyle or metformin for 3 years	58 (lifestyle) 31 (metformin)

benefits were already apparent at one year in the intensive group compared to the conventional group. Overall, the study showed that with this strict regimen five patients need to be treated to prevent one event over seven years.

However, full implementation of such a multifactorial strategy into routine practice remains an ideal: it requires an appropriate multidisciplinary team, as well as the time given by patients. Adherence to multiple therapies and the drug costs for achieving newer and more stringent targets have been identified as barriers. These practical issues concerning the treatment of diabetes are now in a greater spotlight due to the growing number of patients requiring treatment.

## PREVENTING DIABETES

A pragmatic approach to prevent coronary disease in patients with diabetes is actually to prevent diabetes in the first place. Diabetes is rising in prevalence, both nationally and internationally, and is having a major impact upon health care costs. There is now substantial trial evidence showing that the onset of diabetes can be prevented or at least delayed. Several studies since 1997 have used lifestyle or drug interventions and shown a reduction of diabetes by a considerable percentage, as shown in table 4.<sup>23–25</sup>

## CONCLUSION

In an integrated approach to the management of diabetes, it is important to assess cardiovascular risk factors as well as glucose status, to consider lifestyle and diet, and to set goals for treatment addressing both primary and secondary prevention.

Specific therapeutic modalities should be based on both impact and practicality but should address:

- glycaemic control, with a target HbA<sub>1c</sub> of < 7%
- lipid management, with a total cholesterol target of < 5 mmol/L, HDL cholesterol > 1 mmol/L, 10 year cardiovascular risk < 10–15%
- blood pressure control (BP target of < 140/80 mm Hg or < 135/75 mm Hg where microalbuminuria or proteinuria is present)
- aspirin use
- smoking cessation
- weight management and physical activity.

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## DISCUSSION

**Question:** One could assume that in patients with diabetes it would be quite rational, irrespective of their cholesterol concentrations, to treat them as people who have coronary artery disease, even if they do not have a history of angina or myocardial infarction. Should we put them on aspirin, ACE inhibitor and statin straight away to get the ball rolling?

**Dr Feher:** It is a very strong argument. The Americans have actually put this into their national guidance to make diabetes a CHD equivalent. However, I am uncomfortable about using statins just like aspirin, in other words giving the drugs to everyone. I do think that patients need to have a lipid profile measured because some patients do not achieve a target, some people will respond to very low doses of statins while others need higher doses; some people have side effects from statins, and perhaps fibrates may be more appropriate. Statins clearly have benefits, but I cannot support using them indiscriminately. There is strong pressure in diabetes guidelines now to use statins. I would contend that many diabetic patients may need to be on at least one, even two, lipid lowering drugs if we are going to reduce the coronary events significantly.

**Professor Lewis Ritchie (co-chairman):** Basically, the approach you favour is tailored, targeted therapy, “stepping on the gas” as necessary.

**Dr Feher:** Tailoring therapy to the individual is important and this includes diet and lifestyle. The Steno study showed that many patients benefit from dietary and lifestyle intervention although it is a lot of work for three people to spend an hour or two on intervention management every three months.

**Question:** I am a practice nurse and understand why it is so important for many drugs to be used. But if you want

concordance you need patients to feel happy and secure and that they have knowledge about why they are taking these drugs. I see many patients now who do not have a clue what statins are; they have been given a prescription, but they don't really understand why they are taking them. Often they are not happy about the number of drugs they are given, and they either forget or they don't take them for whatever reason. We should not underestimate the importance of the nurse's role in general practice. We need time to educate patients about weight reduction, smoking cessation, and exercise. There needs to be more nurses in general practice doing these things, we do need more health care assistants, and there also needs to be recognition of how well qualified nurses are, and a grading system that is fair.

**Dr Feher:** I entirely agree with that. Diabetes is very complicated to manage properly. Most patients with type 2 diabetes may require up to 6–10 tablets for glucose lowering in addition to appropriate diet. Additional tablets are then required as there is now evidence that glucose control alone is not adequate to prevent coronary disease. Treating the lipid profile and blood pressure are equally as important, perhaps even more so.

**Question:** You asked how we are going to implement these lifestyle changes: four patients on a glitazone pays for one nurse to spend a half-day a week with diabetic patients. It is a matter of where we put our resources. I support the previous questioner and I believe that it will be the nurses leading the way forward.

**Professor Ritchie:** I think the issue relates to the importance of communicating risk to patients: it is not just about what is desirable to do, it is about what the patient's understanding of that is.

**Dr Feher:** Diet and lifestyle modification are the cornerstone of diabetes treatment. This does require appropriate education, and nurses are well placed to educate patients about the condition and the several treatment options.